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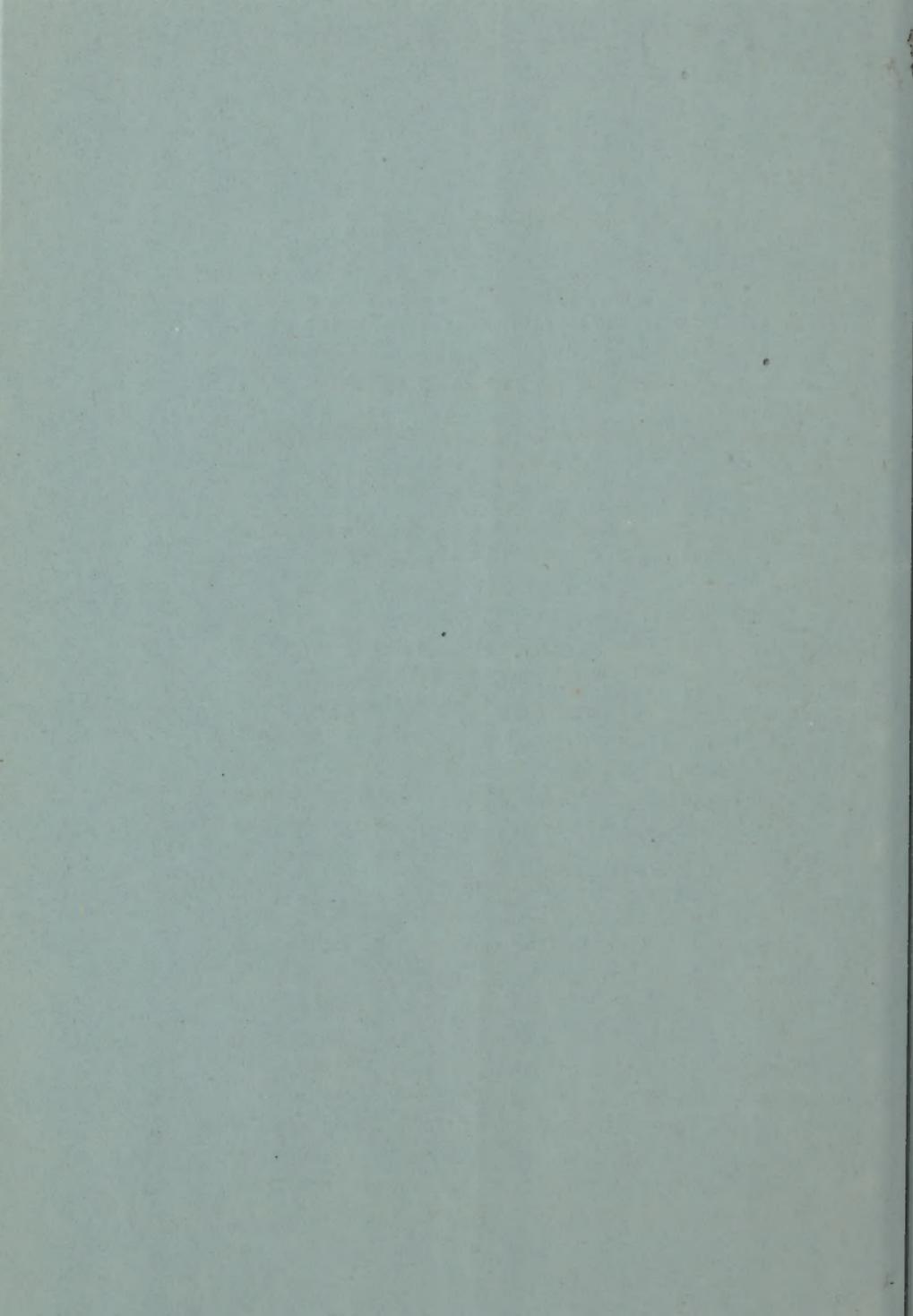
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CHEMISTRY, JEFFERSON MEDICAL COLLEGE, ETC.

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NAPHTHALIN IN TYPHOID FEVER;

Based on Its Employment in One Hundred Consecutive Cases.

BY L. WOLFF, M.D.,

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WITH the recognition of the bacterial origin of typhoid fever and the seat of the characteristic microorganisms in the glandular apparatus of the lower part of the ileum, the endeavor to combat bacterial growth at its peculiar location and thereby to prevent the formation by it of the toxic agents which give rise to the typical symptoms of that disease, intestinal antisepsis soon became a factor in the therapeusis of this affection.

Carbolic acid, thymol, iodine, mercuric and mercurous chlorides and iodides were employed for this purpose, and, with the exception of calomel, were soon relegated to the oblivion they seemed to deserve. That calomel alone remained and proved its worth in practical application, is probably due to its insolubility and its gradual conversion only in the lower part of the small intestines, where it no doubt forms antiseptic compounds. It appears, therefore, that the methods of intestinal antisepsis were not so much at fault as the selection of the



proper antiseptics. Carbolic acid, iodine, thymol, naphthol, corrosive sublimate, etc., are evidently taken up in the upper part of the digestive tract, or early in the digestive act converted into compounds which promptly find their way into the absorbents. In the extreme dilutions in which they can circulate in the blood, even though they were not also promptly eliminated, they cannot possibly exert a sterilizing action on the soil of the bacterial growth. Deducing from the undoubtedly favorable action of calomel in enteric fever, the choice for an intestinal antiseptic should fall upon one that is not readily soluble nor taken up by the absorbents, until it had reached that part of the intestines which is the seat of the etiological microbe. It might be asked, Why not employ calomel, if its action has proven so beneficial? To which must be responded, that its continued use for any length of time is certainly impossible, both on account of its irritant action on the intestinal mucous surfaces, as well as the early-appearing constitutional symptoms, which must at once contra-indicate its employment.

Rossbach, of Jena, some time ago (*Berliner klin. Wochenschrift*, 1884, No. 42) recommended naphthalin as deserving of trial as a suitable intestinal antiseptic agent in typhoid fever, arguing in its favor the good results obtained with it in different enteric affections, both catarrhal and ulcerative. He claimed for it that by its use he was enabled to disinfect the enteric intestinal canal, and that the faeces under its use passed perfectly odorless, or with only a predominating odor of naphthalin. He further claimed for it insolubility in water, acids, and alkalies; also

strong antiseptic powers; and that while toxic in its effect upon insects, it certainly did not exert, even in large doses, toxic or deleterious action upon man. Also, that it was almost always readily tolerated by the stomach, not disturbing the appetite or digestion, and that albumin never appeared in the urine after its use. The same author quotes also the statistics of a number of cases of typhoid fever which had been treated with naphthalin and which had terminated abortively inside of two weeks, while in the late cases it had exerted no marked influence over the disease. In another paper on the same subject (*Berliner klin. Wochenschrift*, 1885, No. 14) he treats further of the action of naphthalin and its untoward effects, and attributes the latter largely to the use of the impure drug or to the idiosyncrasy of the patient. Some of the unpleasant results were strangury, and even præputial edema observed in two tuberculous patients. He already points out the dark coloration of the urine under its use, and thereby admits the elimination of some of it by the kidneys. He claims that the rare untoward symptoms were by far outweighed by the decided beneficial results obtained by its use. In his remarks on this subject at the Congress for Internal Medicine at Berlin in 1884, Rossbach also states that if taken internally it was to some extent eliminated with the urine, either as naphthalin or converted into naphthol, which Baumann and Herter declared was not the case in dogs to which had been given five grammes of naphthalin. They held, therefore, that it must pass off as naphthalin in the aqueous vapors, but did not explain the condition of the organic

sulphates under its use. It was stated by Rossbach that the urine of patients taking naphthalin was preserved from decomposition for weeks ; also, that Schlescher had obtained a naphthol reaction in such urine.

E. Sehrwald, of Jena, in an exhaustive paper on "Naphthalin in Typhoid Fever" (*Berl. klin. Wochenschrift*, 1889, No. 19), from experiments made in the laboratory of the medical clinic of Professor Rossbach, reviews the uses and action of naphthalin, and especially its effect on bacterial life in artificial cultures. He inclines to the view that naphthalin possesses inhibitory action on the development of microorganisms, and though he admits that at ordinary temperature this is very little, he claims to prove that it is increased by greater surface contact, such as might be produced by shaking and peristaltic action ; also, that at the temperature of the body its action on the microorganisms is much more intensive, and that it acts most probably in its gaseous state by inhibiting the growth and is destructive to the life of the germs. It is therefore more energetic on aerobic bacteria and those propagating on solid soil than on the microorganisms vegetating in fluids. He seeks to explain in two ways the beneficial results from naphthalin as an intestinal antiseptic, by the constant peristalsis and the elevated temperature, which causes the fluids thereof to come constantly in contact with the gaseous naphthalin so generated. He states that while the microbes of the faecal masses are by this antiseptic reduced to one-half without the body, they are reduced to one-third or one-fourth in it, and after

evacuation very soon again reach the former proportion. A most significant deduction made by Sehrwald is that naphthalin acts even more forcibly on the typhoid bacilli, reducing them to one-tenth their quantity, and reducing them still further when they have been already reduced by the exhibition of calomel. On account of the mixed character of the infection of typhoid fever and the more energetic manner in which naphthalin acts on the bacilli thereof, and the control of calomel over some of the other bacteria of that disease, he recommends the joint administration of the two drugs in typhoid fever.

Notwithstanding the painstaking experiments of Dr. Sehrwald and his logical deductions, the weak antiseptic powers of naphthalin appear to give no great assurance as to the probable results to be obtained by its use in enteric fever. Having for some time employed naphthalin in the typhoid fever wards of the German Hospital of Philadelphia, and having become satisfied as to its decided beneficial influence on the course of this disease, I have made a number of researches at the laboratory of the Jefferson Medical College as to its action and conversion in the digestive tract. It is hardly to be supposed that we can look for its action as being germicidal when it is at best even a very weak antiseptic. That it is quite insoluble in the fluids of the body would be another objection against its use as an antiseptic. We cannot suppose that it should prove directly antagonistic to bacterial life, but we may infer that, if it were soluble, it should permeate the tissues and transform them into unsuitable soil for microbic

propagation. From Dr. Sehrwald's experiments we would look for the active typhoid bacilli in the contents of the intestines, rather than in the solitary glands and the Peyer's patches of the ileum. What we may look for in the intestinal contents are the soluble products of the pathogenic microbes over which naphthalin or any other antiseptic can have no control; whereas the factors thereof are nested in their glandular beds, propagating there at the expense of the culture soil they offer, and secreting in their destructive process the toxin which gives rise to its pathognomonic symptoms.

It seems to me that an intestinal antiseptic must be intended rather to affect the soil than the bacterium directly, as probably no chemical agent could do this in non-toxic doses. To such an agent naphthalin must be converted before it can produce a local antisepsis and be absorbed. It has been stated by Rossbach that he had given the naphthalin in doses ranging from one and one-half grains to as much as seventy-five grains per day. He urges the larger doses because only with them does the naphthalin become apparent in the faeces. Why should the smaller doses not be eliminated by the bowels, and what becomes of them? To determine this I made, jointly with my assistant, Dr. M. V. Ball, a series of experiments, in which we commenced taking naphthalin in smaller doses, and gradually increasing it until we could demonstrate its presence in the stools in its pure state. We made also control experiments with the stools of typhoid patients, and found that naphthalin in doses not exceeding five grains every four hours would not appear in the

fæces. We further demonstrated that in the five-grain doses the odor of naphthalin was not apparent in the exhalations of the lungs or skin, but that derivatives of naphthalin could be promptly and continuously detected in the urine. The question of the elimination of the naphthalin derivatives from the body has been gone over so extensively, and the tests are so purely chemical, that I will omit them, as they have been published elsewhere by my assistant, Dr. Ball (Prize Essay, Jefferson Medical College, 1889). I will only state that we invariably found naphthol-sulphuric acid, or rather naphthol-sulphurates, in the urine. With ferric chloride they gave a red color, turning to brown, while with diazobenzol-sulphurate of sodium a beautiful red color promptly appeared. From these experiments it may be inferred that in five-grain doses or less all the ingested naphthalin leaves the body in the urine (excepting the probably small quantity escaping in vapor form). This deduction naturally leads to the question of how this conversion of naphthalin can and does take place? It is a well-known fact that in the small intestines there is constantly found and produced more or less hydrogen peroxide, and thence it passes into the blood and even into the urine. It is also a fact that naphthalin forms directly with hydrogen peroxide a hydrate known as naphthol, which, according to its relative position, may be either of the α or β variety, and, furthermore, that the product of naphthalin is a very powerful antiseptic. It may be assumed that it is the naphthol locally produced which exerts the inhibiting power over microbic life, while the value of

naphthalin rests in its being insoluble and being converted only at or near the site of the infection. That it is thence absorbed and eliminated as a sulpho-compound might lead to the question why naphthol itself should not be at once administered. This can be answered to the effect that as naphthol is soluble (about 1 to 1000), it will no doubt be absorbed in the upper portion of the digestive tract, probably little, if any, reaching the lower part of the ileum.

I have made the foregoing experiments and researches to justify my continuance with the treatment of my typhoid patients by this remedy. Before proceeding with my own clinical observations I will quote from the inaugural essay of Dr. Ludwig Wilhelm Goetze, published in the *Zeitschrift für klinische Medicin*, Berlin, 1885, in which he reports thirty-five cases of typhoid fever treated with naphthalin, of which three terminated abortively in three days, ten within ten days, and four within two and one-half weeks; a total of seventeen cases, or 50 per cent of the total number so treated. Of the thirty-five cases three died, so that the total mortality in this series would have amounted to 8.5 per cent. Of these the reporter claims that two deaths were not to be attributed to the typhoid condition, but to severe complications, leaving a mortality of 2.8 per cent. in an epidemic which was considered of a severe type.

My service in the medical wards of the German Hospital during the last three years brought to my observation a rather larger number of cases of typhoid fever than is usually met with in medical

practice. While it is well known that some typhoid epidemics assume a more serious character than others, and that the death-rates vary as a consequence, irrespective of any treatment, I selected for my observations on intestinal antisepsis with naphthalin, one of the more severe, if not the most severe epidemic we had experienced for some years. The cases so treated were selected, but received the same medication, as follows: On admission, calomel with soda was administered in grain doses each three hours for six hours, or until its laxative effect forbade its further use. This was immediately followed by gelatin capsules containing five grains each of purified and finely-powdered naphthalin every four hours, alternated only with a few drops of dilute hydrochloric acid. No other medication was permitted, excepting chemical antipyretics and cold sponging for hyperpyrexia. The diet consisted of milk, alternating with meat broths containing raw eggs; stimulants were administered as required.

I submit herewith a *résumé* of one hundred consecutive cases treated in this manner. An analysis of this series of cases shows the following results: Of the one hundred patients fifty-six were males and forty-four females; their average age was 24.7 years; the mean duration of the febrile period was 24.4 days: this may seem large, but when we take into consideration that some had long sieges of fever and others had two or three relapses, it explains the reason for such a protracted average fever period. A notable fact is that in the one hundred patients so treated sixteen cases ran an abortive course, *i. e.*, they defervesced before the end of the

second week. Only three of the patients had intestinal haemorrhage, which, however, in two of the cases occurred shortly after they were transferred to me and subjected to naphthalin treatment. The total mortality was 10 per cent. Two cases were brought in comatose and never rallied, and died within three days after admission. Of the complications resulting in death was one with facial erysipelas, one with glosso-pharyngeal paralysis, one with acute pulmonary phthisis, one from heart failure in consequence of valvular heart lesion. Of the other four remaining fatal cases, two died respectively within four and five days after admission, never having responded to treatment. I may, from the foregoing, fairly assume that the mortality of these cases under naphthalin treatment did not exceed 2 per cent. It is not probable that the total death-rate from typhoid fever in general hospitals will ever be reduced much below 10 per cent., as severe cases admitted late in the disease, or with complications which no longer admit of treatment at their homes, will under any treatment prove more or less fatal.

To understand the value of my figures here given I must refer to the death-rate of typhoid fever at the German Hospital of Philadelphia for the five years prior to the epidemic during which I made the observations the results of which I have herein submitted. According to the statistics of this hospital the death-rate from typhoid fever in 1884 was 23.4 per cent.; in 1885, 11.4 per cent.; in 1886, 20.4 per cent.; in 1887, 17.4 per cent.; and in 1888 it was 13.2 per cent.; while the one

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hundred cases which I have here reported followed in 1889 with a total death-rate of 10 per cent. As a comparison made of the death-rates under various treatments I can quote no better statistics than those of Liebermeister, in Basle, which he gives as follows :

On the indifferent plan, 27.3 per cent. ; on incomplete antipyretic treatment, 16.2 per cent. ; on complete antipyretic treatment, 10.2 per cent. ; no specific treatment, 28.7 per cent. ; calomel treatment, 12.4 per cent. ; iodine treatment, 12.9 per cent.

As a result of my observations I would also state that naphthalin has no direct influence on the fever temperature ; it is often surprising, however, how soon after its continued administration a lysis will take place and a normal temperature will be reached. That this is due to the inhibiting effect of the drug on the morbid process and its etiological elements may be inferred from the fact that if in such cases the medication be discontinued directly on defervescence, a renewal of the febrile process will generally take place. It was at first a matter of some surprise that the relapses were so frequent, there being nine cases showing renewal of fever and some of them had even two and three relapses. After that, I continued the naphthalin for some time after complete defervescence, and the frequency of relapses was greatly diminished. In only one of the cases did I find continued nausea and persistent vomiting, necessitating an interruption in the naphthalin treatment, which, however, was resumed subsequently without further trouble. One of the favor-

able results of naphthalin treatment is the control it exerts over the excessive and exhausting diarrhoea. After its continued use for some time it may even be found necessary to administer laxatives or exhibit laxative enemata to overcome resulting constipation. There seems to be no repugnance on the part of the patient against the drug, unless it is administered in suspension instead of in gelatin capsules. The appetite is in no manner impaired by it, and I have had no occasion to observe any irritation of the uropoëtic apparatus with the purified naphthalin I invariably employed. I have carefully watched its effect on the heart, but found that it is in no way impaired or depressed by it.

In conclusion, I may sum up my deductions as follows: That the treatment of typhoid fever should always be under two heads—one for the infection and the other for the toxæmia resulting therefrom. There seems to me no room for doubt that at the onset of the disease the administration of naphthalin may inhibit the development of the pathogenic microbes to such an extent that the fever itself will run an abortive course. Further, that at any period of the disease we may restrict the growth of the etiological factors in a measure, that an over-production of the chemical toxins may be prevented, and thus the fever run a mild course. This is possible, in my estimation, only with chemical agencies which, innocent in their immediate action on the organism, will be chemically altered in the lower part of the digestive tract, and there exert their antisепtic action on the soil of the pathogenic microorganisms. Of these agencies naphthalin

and calomel are the principal representatives, and of the two, naphthalin must have the preference for its non-toxic character. Whether naphthol directly administered in keratin-coated pills be preferable, I am not prepared to state, although I know that, if ingested in suitable quantities for intestinal antisepsis, it produces local irritation, reflex vomiting, and diarrhœa. The gradual but continued development of naphthol from naphthalin *in situ* seems more calculated to produce intestinal antisepsis without the accompanying irritation of masses of naphthol.

Although I feel justified from the foregoing in recommending the use of naphthalin for the treatment of the specific infection of typhoid fever, I do not wish it to be understood that I recommend it as the sole treatment of this disease. No chemical agent so far known can destroy the characteristic toxins without also destroying life, and naphthalin can in no manner influence the already absorbed typhotoxin nor combat the symptoms it produces. For the toxæmia there is no specific remedy save speedy elimination and the stimulation of the vital organs against it. Though not within the province of my paper, I would say that, in my opinion, this is best obtained by cold baths; but I should think myself as much remiss to depend upon combating simply the specific poison in the body without attempting to limit its production, as I would be by attending to intestinal antisepsis alone without regard to the dangerous symptoms which the absorbed poison has already produced.

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